

# Physiology of the Hypothalamic Pituitary Gonadal Axis in the Male



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## KEYWORDS

- Testosterone • Gonadotropin • Hypogonadism • Primary hypogonadism
- Secondary hypogonadism • Hypogonadotropic hypogonadism

## KEY POINTS

- Testosterone synthesis and male fertility are controlled by a negative feedback mechanism between the hypothalamus, the pituitary, and the testis.
- Congenital or acquired conditions leading to a failure of hormone synthesis or action at any level of the hypothalamic-pituitary-gonadal axis result in the clinical syndrome of hypogonadism.
- Medications and contemporary diseases are major causes of impairment of male reproductive function. Novel therapies may improve spermatogenesis along with elevating testosterone levels in men.

## INTRODUCTION

Reproductive function changes markedly during life in humans. Impeccable coordination of the hypothalamic-pituitary-gonadal axis is required for normal testicular function in the male, including normal testosterone production and male fertility. Pulsatile secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus stimulates the biosynthesis of pituitary gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) that, in turn, sustain intragonadal testosterone production and spermatogenesis. A negative feedback mechanism, controlled by sufficient levels of testosterone, is responsible for decreasing both hypothalamic GnRH secretion into the portal circulation and gonadotropin release from the pituitary into the bloodstream.

Congenital or acquired conditions leading to a failure of hormone synthesis or action at any level of the axis result in the clinical syndrome of

hypogonadism. Hypogonadism may be caused either by a primary testicular disease or by a secondary (or central) cause (eg, a hypothalamic or pituitary disorder). In the setting of acquired hypogonadism, comorbidities and use of medications are common causes of low testosterone and must be ruled out before making the diagnosis.

Despite the cause, end organ replacement therapy with natural testosterone is recommended for chronic use but with the understood general caveat that this treatment does not improve fertility. If medications that stimulate hypothalamic or pituitary function are successful, these agents may be used for several-month intervals to enhance spermatogenesis; however, their long-term use needs further investigation. In addition, novel therapeutic agents have been proposed to stimulate both testosterone and spermatogenesis. The understanding of hypothalamic-pituitary-gonadal axis physiology is the first step for the correct diagnosis

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and treatment of hypogonadism, a frequent condition affecting quality of life and causing other comorbidities including osteoporosis in men.

This article reviews the physiology of the brain-hypothalamic-pituitary-gonadal axis, to correlate it to disorders that can induce male hypogonadism, and discusses available and potential future treatment modalities.

## ANATOMIC OVERVIEW OF THE HYPOTHALAMUS AND PITUITARY

The hypothalamus lies at the base of the brain, below the thalamus and the third ventricle, just above the optic chiasm and pituitary gland. It synthesizes and secretes certain neurohormones, often called *releasing hormones* or *hypothalamic hormones*, and these in turn stimulate or inhibit the secretion of pituitary hormones. The neurovascular link between hypothalamus and pituitary gland is the pituitary stalk, which comprises mainly neural and vascular components.

The pituitary gland, also known as the *hypophysis*, is located immediately beneath the hypothalamus, resting in a depression of the base of the skull called the *sella turcica* (Turkish saddle). The pituitary gland is entirely ectodermal in origin but is composed of 2 functionally distinct structures that differ in embryologic development and anatomy: the adenohypophysis (anterior pituitary) and the neurohypophysis (posterior pituitary). The adenohypophysis develops from an upward invagination of oral ectoderm named *Rathke's pouch*, whereas the neurohypophysis derives from a downward extension of neural ectoderm, the infundibulum.<sup>1</sup> Because the pituitary is just below the crossing of the visual nerves at the optic chiasm, pituitary tumors enlarging superiorly may affect superior temporal vision selectively.

The adenohypophysis is the manufacturer of an array of peptide hormones—gonadotropins (FSH and LH), adrenocorticotropin, growth hormone, prolactin, and thyroid-stimulating hormone (TSH)—and makes up roughly 80% of the pituitary gland. The release of these pituitary hormones is mediated by hypothalamic neurohormones that reach the adenohypophysis via a portal venous system.

Unlike the adenohypophysis, the neurohypophysis is not glandular and does not synthesize hormones. It stores and releases oxytocin and vasopressin, which are synthesized by neurosecretory cells of the hypothalamus. The neurohypophysis comprises axons of hypothalamic neurons; the neurohypophysis is, therefore, considered an extension of the hypothalamus.

## CONTROL OF HYPOTHALAMIC SECRETION

In recent years, kisspeptin, a 54-amino-acid peptide, encoded by the *KISS-1* gene, was identified. Kisspeptin activates the G protein-coupled receptor (GPR54) of the hypothalamus. During pregnancy, kisspeptin levels increase 7000 times. Human placenta secretes varying lengths of the peptide, but the C-terminal 10-amino-acid portion is sufficient to activate GnRH receptors in the fetus, initiating function of the hypothalamic-pituitary-gonadal axis. Kisspeptin also provides the major trigger for puberty. In rat studies, chronic infusion of kisspeptin triggers precocious puberty and enables pubertal development in undernourished animals.<sup>2</sup>

## NORMAL HYPOTHALAMIC REGULATION OF GONADOTROPINS

Secretion of pituitary gonadotropic hormones is regulated by the hypothalamic decapeptide hormone, GnRH, which binds to a membrane receptor on pituitary gonadotrophs, stimulating synthesis and secretion of both FSH and LH, the 2 pituitary gonadotropic hormones (**Fig. 1**).

Animal studies found that, in GnRH-deficient mice, pretreatment with GnRH led to both an increase in the gonadotropin content of the pituitary gland and<sup>3</sup> an induction of the expression of pituitary GnRH receptors.<sup>4</sup> Under certain physiologic conditions, GnRH receptor number varies and usually directly correlates with the gonadotropin secretory capacity of pituitary gonadotrophs.

Besides the number of GnRH receptors, pulsatile regimens of GnRH are required for the precision of pituitary gonadotropin signaling.<sup>5</sup> GnRH pulsatility seems to be an intrinsic function of hypothalamic cells, dependent on calcium, with communication similar to nerve synapse conduction.<sup>6</sup> Studies find a sequential response of gonadotropin secretion after exogenous GnRH administration in GnRH-deficient mice; there is an immediate and persistent increase in plasma FSH concentrations during the period of GnRH injections, whereas LH secretion requires a more prolonged and pulsatile GnRH therapy before LH is detected in the circulation.<sup>7</sup> Furthermore, these important data indicate that FSH continues to be synthesized and stored even in the absence of sustained GnRH administration, but continued GnRH stimulation is required for LH synthesis.

## FOLLICLE-STIMULATING HORMONE, LUTEINIZING HORMONE, AND TESTICULAR FUNCTION

FSH and LH are heterodimers with structural similarities; each consists of  $\alpha$  and  $\beta$  peptide

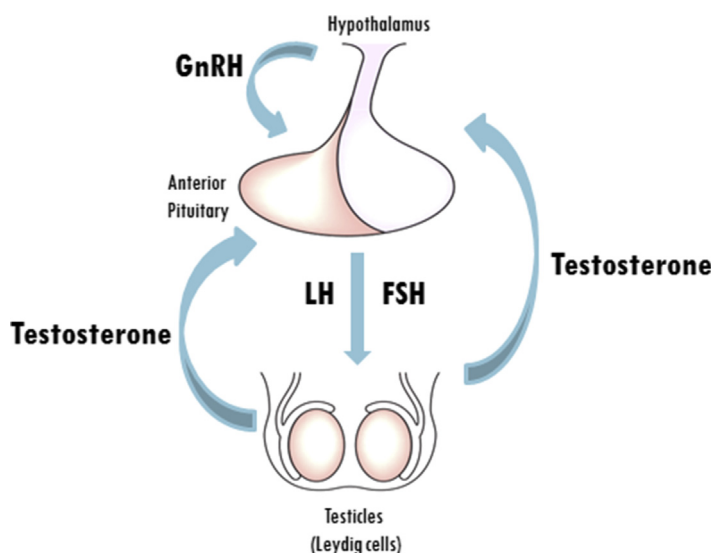


Fig. 1. Hypothalamic-pituitary-gonadal axis.

chain subunits, produced in the pituitary of both men and women. The  $\alpha$  subunit is identical in both hormones; the  $\beta$  subunit, therefore, provides structural and biochemical specificity for receptor interactions and also determines the biologic specificity of the hormone. To date, hypogonadotropic hypogonadism (HH) owing to selective mutations in the FSH  $\beta$  or LH  $\beta$  subunit genes is rarely reported.<sup>8</sup>

FSH is required for the determination of the testicular Sertoli cell number and for induction and maintenance of spermatogenesis. In testes with a sufficient level of testosterone,<sup>6</sup> LH stimulates the secretion of gonadal steroids through Leydig cell activity. The same LH molecule stimulates estradiol synthesis in the ovary in women.<sup>9</sup> By activating the FSH receptor, FSH has specific function within the Sertoli cells of the testis, resulting in an increase in cyclic adenosine monophosphate, thereby activating a cyclic adenosine monophosphate-dependent protein kinase. This increase, in turn, increases protein synthesis of androgen-binding protein (sex hormone-binding globulin [SHBG]) and the aromatase enzyme CYP19, which converts testosterone to estradiol.<sup>10</sup>

Steroidogenesis, under the influence of LH acting through specific receptors found on the surface of the testicular Leydig cells, stimulates enzymatic conversion of precursor cholesterol into testosterone. Leydig cell secretion creates a high local concentration of testosterone in the testis; testosterone is also secreted into the circulation, with circulating testosterone levels occurring in a steep downhill concentration gradient from the testes, producing characteristic androgenic

effects on distant androgen-sensitive target tissues.<sup>11</sup> When testosterone levels are sufficient, the pituitary gland decreases the production and release of LH via a negative feedback mechanism, which also decreases GnRH and LH, thereby, decreasing testosterone levels. Apparently, much of the negative feedback regarding FSH occurs via the gonadal peptide hormones, inhibins, and activins, members of the transforming growth factor- $\beta$  super family of molecules. Sertoli cells of the adult testes secrete both inhibins A and B, but the more important hormone is inhibin B, which suppresses FSH secretion, modulating the FSH stimulation by activins. Follistatins, produced within the pituitary, bind activins and further decrease their function. Beyond their negative pituitary feedback, inhibins function also throughout the reproductive hormonal axis and act locally as paracrine hormones within the testes.<sup>12</sup>

### PERIPHERAL METABOLISM OF TESTOSTERONE

The testis contributes more than 95% of total circulating testosterone in the postpubertal man (the adrenal contributes the remainder). Testosterone is secreted into the circulation down a concentration gradient, where it equilibrates between protein-bound (98%) and free hormone (2%) fractions. Protein-bound testosterone binds either to low-affinity, high-availability proteins (primarily albumin) or to the high-affinity, low-abundance SHBG, a glycoprotein. The free hormone fraction is generally believed to be the biologically active form of testosterone. Once released in the

bloodstream, testosterone reaches its peripheral sites of action, where it undergoes reversible and irreversible metabolism to other steroids with different activities (Fig. 2).

Although only approximately 5% of serum testosterone produced in men undergoes  $5\alpha$ -reduction to dihydrotestosterone (DHT), many of the important functions of testosterone are mediated by this potent metabolite.<sup>13</sup> Testosterone and DHT bind to a common androgen receptor; however, DHT has 2 to 3 times greater androgen receptor affinity than testosterone; moreover, the dissociation rate of testosterone from the androgen receptor is 5-fold faster than DHT.<sup>14</sup> Also, DHT cannot be aromatized to estrogen. During embryogenesis, DHT has an essential role in the formation of the male external genitalia, whereas in the adult, DHT acts as the primary androgen in the prostate and in hair follicles.<sup>15</sup> If there is insufficient conversion of testosterone to DHT, owing to deficient  $5\alpha$ -reductase enzyme, as in the genetic “penis at 14” syndrome ( $5\alpha$ -reductase deficiency), the infant male will have a feminine appearance with small phallus and internal testes. However, after puberty, the penis enlarges and the male appearance ensues under the influence of mature testosterone levels.<sup>16</sup> Interestingly, this gender transformation is completely accepted socially and psychologically in certain inbred communities of the Dominican Republic and Greece, and the adult male has normal reproductive

function. (As a matter of fact, this issue is accurately addressed in the Pulitzer Prize-winning novel *Middlesex*, by Jeffrey Eugenides published in 2002.)

In the adult, as testosterone is converted to DHT, the prostate gland grows and male pattern hair loss proceeds. Understanding this biology, drug blockade with a  $5\alpha$ -reductase antagonist like finasteride may be used to decrease prostate size in benign prostatic hypertrophy and to slow male pattern balding.<sup>17</sup> This drug is dangerous for a pregnant woman to use, as it would also impair the development of a phallus in the male fetus, similar to the block in the previously mentioned “penis at 14” syndrome.

In peripheral tissues, testosterone can also be converted to estrogens through the action of microsomal P450 enzyme CYP19 aromatase, expressed in many sites, including placenta, gonads, brain, and fat. More than 80% of circulating estradiol in men is derived from the aromatization of testosterone<sup>18</sup>; thus, male hypogonadism leads to a consequent hypoestrogenism. In men with deficient aromatization of testosterone to estrogen, there are high levels of testosterone, yet decreased levels of estrogen lead to increased levels of LH, a demonstration that lack of estrogen feedback to the pituitary is more important than feedback from testosterone.<sup>19</sup> Together with evidence of the important role of estrogen in bone metabolism, Finkelstein and colleagues<sup>20</sup> found

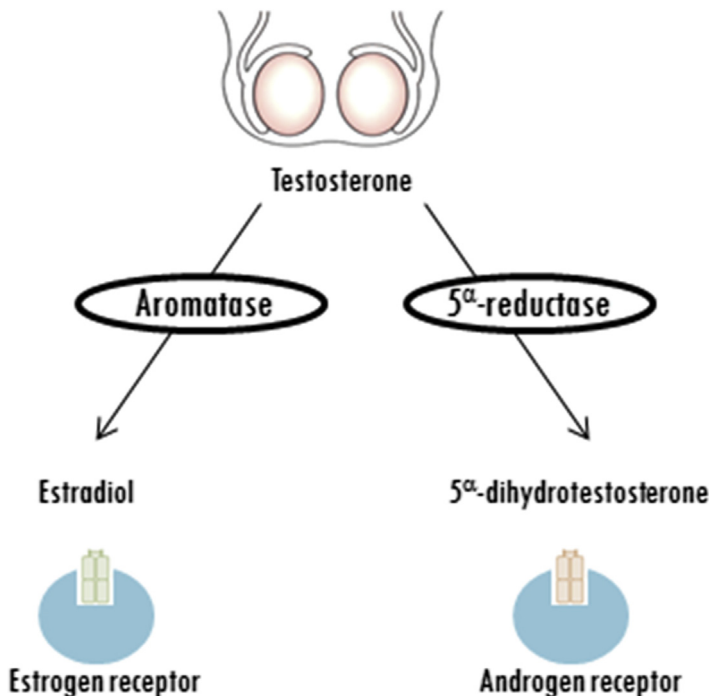


Fig. 2. Peripheral testosterone metabolism.

that estrogens also play a fundamental role in the regulation of body fat and sexual function in men. On the other hand, in situations of fat accumulation, such as obesity or insulin resistance, the increased adiposity is associated with increased aromatase conversion of testosterone to estrogens in fat tissue, often resulting in gynecomastia, sometimes with lower levels of testosterone.

## SEXUAL DEVELOPMENT IN MALES

Pulsatile secretion of GnRH from the hypothalamus is required for the maintenance of reproductive function; however, the pattern of GnRH-induced gonadotropin secretion is constantly changing during sexual development. Neuroendocrine stimulation of the reproductive axis is initiated during fetal development. Although GnRH neurons are seen earlier in fetal life, the connection between these neurons and the portal system of the hypothalamus and pituitary becomes functional around 16 weeks of gestation.<sup>21</sup> Hypothalamic GnRH neurons are functional at birth but, after the perinatal androgen surge, remain tonically suppressed during infantile life. During childhood, the hypothalamic-pituitary axis is characterized by low pulse frequency and low amplitude GnRH secretion.

The precise neuroendocrine trigger of puberty is not fully understood. Nevertheless, its onset is marked by sleep-entrained reactivation of the reproductive axis characterized by a remarkable increase in the amplitude of LH pulses with a lesser change in frequency. Initially, the nighttime elevation of LH secretion stimulates gonadal secretion of sex steroids, which return to prepubertal levels during the daytime. As puberty progresses, gonadotropins are secreted during both day and night, allowing sexual development to be completed.<sup>22</sup> The testicular output of testosterone gains control over the hypothalamic discharge of GnRH, maintaining a constant frequency of LH pulses, and the sleep-entrained differences in testosterone and LH become negligible. By this time, the increased level of testosterone, along with its conversion to the active metabolite DHT, causes deepening of the voice, secondary sex hair distribution, enlargement of testicles, growth of the penis, and increased libido. Higher levels of testosterone itself, and by its conversion to estrogen, lead to development of muscle mass, bone maturation, and accelerated bone growth until closure of the epiphyses of long bones.

During adulthood, pulsatile GnRH continues to stimulate biosynthesis of LH and FSH that, in turn, sustain intragonadal testosterone production

and spermatogenesis as well as systemic testosterone secretion and virilization.

## HYPOGONADOTROPIC HYPOGONADISM

Failure of the episodic GnRH secretion or action, or disruption of gonadotropin secretion, results in the clinical syndrome of HH. This condition can be caused by either pituitary or hypothalamic disorders and is referred to as *secondary* or *tertiary* hypogonadism, respectively. Secondary and tertiary HH can be distinguished from primary or testicular causes by the demonstration of low/normal gonadotropin levels in the setting of low testosterone concentration (**Table 1**).

A high number of loci are associated with congenital GnRH deficiency and mutations in the GnRH receptor in the pituitary. The mutated GPR54 receptor, not receptive to kisspeptin stimulation, may cause HH in humans.<sup>2</sup>

Although rare, congenital abnormalities are well understood and described causes of deficient GnRH secretion and can occur either in isolation (normosmic congenital HH) or in association with anosmia or hyposmia, which is named *Kallmann syndrome* (KS). To define the genetic and phenotypic variability of GnRH deficiency syndrome in humans, a detailed family history of 106 GnRH-deficient patients collected by Waldstreicher and colleagues<sup>23</sup> found an equal occurrence of KS and idiopathic HH. Their observations in this cohort of patients found the predominance of males (85 males vs 21 females) and the autosomal transmission in familial cases. Despite prior studies suggesting an X-linked form of KS, in this series, this finding was not consistent. Therefore, they concluded that most often, this abnormality occurred sporadically, and many were novel autosomal mutations.

On immunoreactive labeling, normal and KS human nasal epithelium obtained from aborted human fetuses contains both sex steroid (estrogen and progesterone) and GnRH receptors. Because the olfactory neurons and GnRH neurons have a common embryologic origin, the congruence of GnRH deficiency and anosmia as related abnormalities of neuronal migration from the cribriform plate through the olfactory bulb and tract to the hypothalamus during organogenesis is not surprising. One of the mutations identified in X-linked KS is in the *KAL1* gene, encoding anosmin-1, a neural cell adhesion glycoprotein critical to growth and movement of the GnRH neurons.<sup>24</sup> Abnormalities affecting *pKAL*, the promoter region of this gene, have also been found. Absent olfactory tracts may be found on brain MRI (see **Fig. 4**).<sup>25</sup> The interconnected nature of smell and sex hormone control

**Table 1**  
**Causes of hypogonadism in males**

Primary (Increased LH/FSH, Low T)		Secondary (Normal/Low LH/FSH, Low T)	
Congenital	Acquired	Congenital	Acquired
Klinefelter syndrome	Chronic renal failure	KS	Hyperprolactinemia
Androgen synthesis disorder	Hepatic cirrhosis	DAX-1 mutation	Critical illness
Mutation of FSH receptor gene	Hemochromatosis	GPR-54 mutation	Chronic systemic illness
Cryptorchidism	Human immunodeficiency virus/AIDS	Leptin or leptin receptor mutation	Diabetes mellitus
Undescended testicles	Infections (eg, mumps orchitis)	Prader-Willi syndrome	Obesity
Varicocele	Radiation	Gonadotropin subunit mutation	Neoplasms
Myotonic dystrophy	Trauma		Infiltrative diseases (eg, sarcoidosis, histiocytosis, tuberculosis)
	Toxins (eg, ethanol)		Pituitary apoplexy
	Autoimmune damage		Pituitary trauma
	Drugs		Ethanol
			Drugs

Abbreviation: T, testosterone.



was shown by demonstration that human fetal olfactory reception provokes GnRH gene expression with GnRH protein secretion (Even later, in adult mammals, the sense of smell, transmitted by pheromones, may lead to perception of ovulatory status and elicit reproductive behaviors).<sup>26</sup> Along with low testosterone, decreased fertility, and anosmia, KS individuals may have other neurologic changes and cardiac conditions.

Rare mutations of the LH- $\beta$  or FSH- $\beta$  subunits cause resistant syndromes. Acquired causes of HH are far more common and may be caused by any disorder that affects the hypothalamus itself. In adults, HH can be induced by emotional stress, physical exercise, anorexia, sleep deprivation, alcohol, and medications (**Box 1**). The hypothalamus, in turn, is controlled by brain centers responding to stimulation from the environment affecting mood and status. For example, recent studies found that fatherhood may lower testosterone levels,<sup>27</sup> whereas situations in which an individual is angry or exerts power might increase testosterone levels.<sup>28</sup>

Aging, obesity, and type 2 diabetes are known risk factors for hypogonadism in men. Studies have found that testosterone production slowly and continuously decreases as a result of aging, although the rate of decline varies, unlike women, who experience a rapid decline in sex hormone levels during menopause. Both cross-sectional and longitudinal studies found a decline in serum testosterone concentration, an increase in SHBG concentration, and a decrease in free testosterone with age. Also, a significant percentage of men older than 60 years have serum testosterone levels that are less than the lower limits of young adult (age 20–30 years) men.

Similar to the projections for an aging population, an increased incidence of secondary hypogonadism can be a result of the increasing incidence

of obesity. The proposed causes for the effects of obesity on testosterone levels include increased clearance or aromatization of testosterone into estrogen in the adipose tissue (see **Fig. 2**) and increased formation of inflammatory cytokines, which hinder the secretion of the GnRH.<sup>29</sup> Another common cause of hypogonadism, diabetes mellitus, was found to be associated with primary testicular failure and low testosterone levels and also may produce HH with low pituitary gonadotropin levels.<sup>30</sup>

Some drugs, including synthetic anabolic steroids and other corticosteroids, may result in hypogonadism with decreased endogenous male hormone production and reproductive failure. The negative hypothalamic-pituitary feedback from exogenous androgens causes a functional form of HH, and the decreased gonadotropin secretion, in turn, lowers both endogenous testosterone and DHT secretion and impairs spermatogenesis, shrinking testicular volume and decreasing fertility.<sup>31</sup> Simultaneously, well-described side effects include loss of libido, erectile dysfunction, gynecomastia, increased acne, profuse sweating, and increased prostate size.

The effects might be the same if an exogenous testosterone product (intramuscular or transdermal) is used. If a 5 $\alpha$ -reductase inhibitor is used at the same time as the androgen, male pattern hair loss does not proceed. In addition, testosterone alone or testosterone administered in combination with the 5 $\alpha$ -reductase inhibitor, finasteride, is associated with similar increase in hematocrit and incidence of polycythemia.<sup>32</sup> A thorough medical history in the hypogonadal man should include the use of exogenous synthetic or natural androgens.

## ANDROGEN INSENSITIVITY SYNDROME

Androgen insensitivity syndrome is the largest single entity that leads to male undermasculinization.<sup>33</sup> Androgen insensitivity syndrome can be defined as an X-linked disorder caused by mutations in the androgen receptor gene that lead to complete or partial resistance to the biological actions of androgens in an XY boy or man with normal testis determination and production of age-appropriate androgen concentrations.

In the complete form of androgen insensitivity, the phenotype is a complete feminization of an XY individual. Androgen insensitivity is often diagnosed by chance, during the investigation of primary amenorrhea in adolescence, or inguinal swellings in an infant. The presence of undescended testis is associated with abnormal

### Box 1 Medications that could potentially cause hypogonadism

Glucocorticoids  
Ketoconazole  
Chemotherapeutic drugs (eg, alkylating agents)  
Opiates  
GnRH analogues  
Anabolic steroids  
Metoclopramide  
Spironolactone

testicular development and an increased risk of germ cell malignancy.<sup>34</sup> When complete androgen insensitivity is diagnosed in infancy, early gonadectomy with puberty induction can be done later, or gonadectomy can be delayed until early adulthood, as clinical studies find that the risk of premalignant change in germ cells is low before and during puberty.<sup>35</sup> Hence, feminizing hormone therapy is required to induce or maintain secondary sexual characteristics. Estrogen is also important to optimize bone mass accrual.<sup>36</sup>

The clinical presentation of partial androgen insensitivity syndrome varies according to the degree of responsiveness of the external genitalia to androgens. Therefore, the determination of gender to be raised is usually determined by the dominant phenotype.

Androgen insensitivity presents with an endocrine profile of a hormone-resistant state: testosterone levels are either within or greater than the normal range for men and boys, and LH concentrations are inappropriately increased. Concentrations of FSH and inhibin are generally normal. Serum anti-Müllerian hormone measurement suggests the presence of testes.<sup>37</sup>

## ABNORMALITIES IN TESTICULAR FUNCTION

The control of gonadotropin production, with negative feedback, can be seen in Klinefelter syndrome. Klinefelter syndrome is characterized by the presence of one or more extra X chromosomes, and the karyotype 47 XXY or variants XXY/XY or XXXY. It is the most common chromosomal abnormality with a prevalence of 1:600 in males in some series; Klinefelter syndrome is the most common genetic cause of small testis and azoospermia.<sup>38</sup> The testicular histology of Klinefelter patients is somewhat variable but often includes progressive hyalinization of the seminiferous tubules with age-related loss of germ cells,<sup>39</sup> with Leydig-cell hyperplasia yet inefficient androgen production by Leydig cells.<sup>40</sup> Because of this extensive testicular involvement, gonadotropin levels increase, the LH responding to the low level of negative feedback from testosterone. At the same time, perhaps in response to abnormal spermatogenesis, FSH secretion is stimulated, resulting in high plasma levels of FSH.

In several described cases, testosterone synthesis is impaired owing to abnormalities of the LH receptor gene, leading to LH resistance in the testes with Leydig cell hypoplasia. Affected XY patients present with variable fetal development of masculine features (ie, micropenis, feminized external genitalia) and primary hypogonadism. In

this condition, the LH level is high, although testosterone level remains low in the plasma.<sup>41</sup>

Cancer treatment also has influence on the male reproductive system. Some chemotherapeutic agents and radiation therapy can induce infertility by damaging the seminiferous tubules and by damaging spermatogonia.<sup>42</sup> Concomitant weight loss may further damage the hypothalamic-pituitary-testicular axis.

## DIAGNOSIS

Gonadal steroids regulate pituitary gonadotropin secretion in part by altering the amplitude or frequency of hypothalamic GnRH release.<sup>5</sup> The presence of such a negative feedback control by the testis on pituitary FSH and LH secretion is best shown by the rapid increase of FSH and LH after castration. Given its short half-life, in the adult male, LH is secreted in pulses approximately every 2 hours.<sup>43</sup> However, considerable variability is observed in LH pulse patterns, and there is a wide range of testosterone secretory patterns. Comorbidities, infections, and concomitant use of drugs that could alter hormonal synthesis or secretion at any axis level must be ruled out. Also, within-patient variation must be considered when interpreting single LH and testosterone measurements obtained during the evaluation of a male with suspected hypogonadism. Young men exhibit a diurnal variation, with highest values of testosterone at about 8 AM and lowest about 8 PM, but older men have little variation.<sup>44</sup> Sometimes men who are found initially to have a low testosterone concentration will have a normal level on repeat early morning testing.<sup>45</sup>

The diagnosis of androgen deficiency should be made only in men with consistent symptoms and signs (**Box 2**) and unequivocally low early-morning serum testosterone levels that are less than the lower limit of the normal range (usually <300 ng/dL)<sup>46</sup> in at least 2 different morning measurements. Free or bioavailable testosterone levels may be useful in men with suspected SHBG abnormalities caused by aging, obesity, chronic illness, thyroid disease, or liver disease.<sup>47</sup> Gonadotropins should be measured to elucidate the integrity of the central portion of reproductive axis. Additional pituitary hormone testing, such as an elevation of prolactin, may be useful to confirm a diagnosis of secondary hypogonadism with pituitary disease. In HH, stimulation with GnRH (also called LHRH) infusion to see pituitary gonadotropin (LH and FSH) response is useful to separate hypothalamic causes that do respond from the nonresponsive pituitary causes.<sup>48</sup> Karyotyping should be used to exclude Klinefelter



**Box 2****Signs and symptoms of hypogonadism in the adult male**

Sexual dysfunction: reduced libido, diminished penile sensation, erectile dysfunction, difficulty attaining orgasm, reduced ejaculate, oligospermia

Regression of secondary sexual characteristics

Reduced bone mass or bone mineral density

Muscle wasting

Gynecomastia

Reduced energy, fatigue

Anemia

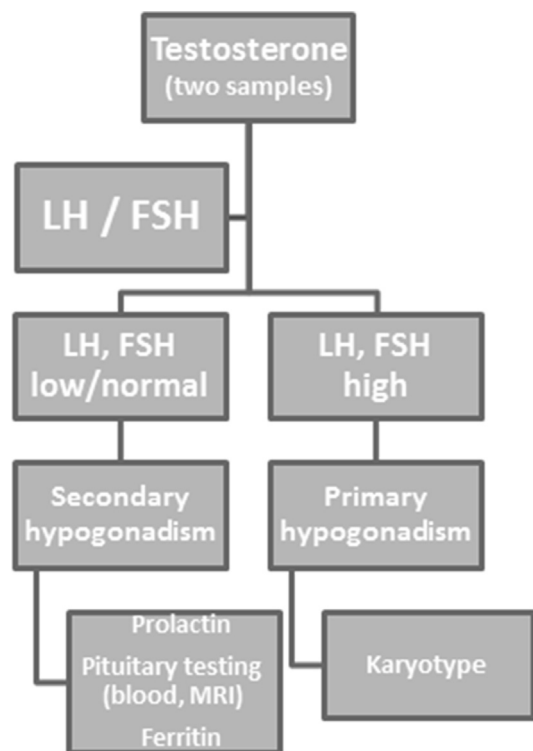
Increased abdominal adiposity

Depressed mood

Difficulty concentrating

Changes in cholesterol levels

syndrome in the suspected individual (Fig. 3). Pituitary MRI may find pituitary and hypothalamic disease and even show the absence of olfactory structures in KS (Fig. 4).<sup>24</sup>



**Fig. 3.** Algorithm for clinical diagnosis of hypogonadism.

**TREATMENT**

Once hypogonadism is diagnosed, chronic hormone replacement is the preferable therapy using testosterone preparations. Nevertheless, because exogenous testosterone formulations cannot mimic the natural endogenous pathway of hypothalamus-pituitary hormonal axis, suppression of the hypothalamic-pituitary-gonadal axis is inevitable via a negative feedback mechanism. Low levels of GnRH, in turn, further decrease production of LH and FSH by the pituitary gland. The low LH levels translate to low testosterone production by the Leydig cells in the testis.

If prolactin is elevated, dopaminergic drugs including bromocriptine or cabergoline may be used to suppress prolactin and often enhance gonadotropin secretion.

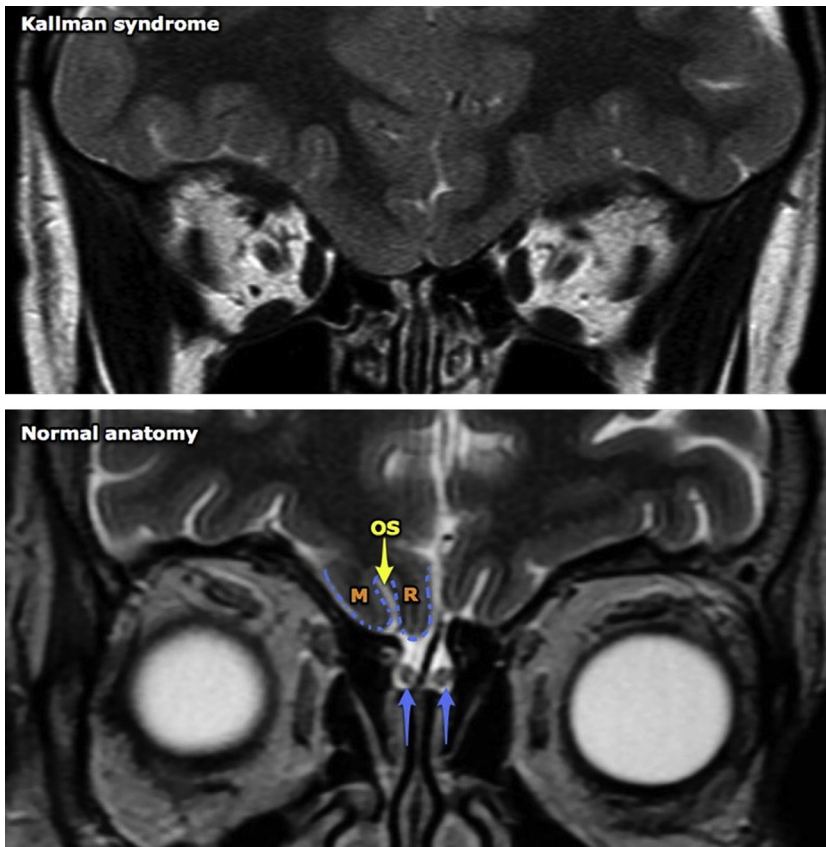
LH and human chorionic gonadotropin (hCG) are heterodimeric glycoproteins that share a common  $\alpha$  subunit. The rate-limiting step in LH and hCG production is the transcription of the  $\beta$  subunit. They have different stability, circulating half-life, and affinity to receptor; however, as a result of minimal structural differences, they both bind and activate a common receptor in the gonads. Although each hormone triggers a particular cascade of events after receptor binding,<sup>49</sup> pharmacologic hCG functions as an LH analogue and is known to stimulate testosterone synthesis in Leydig cells.<sup>50</sup>

In patients who have undergone hypophysectomy, or in other pituitary diseases, often hCG alone can sustain spermatogenesis.<sup>51</sup> Men must continue subcutaneous or intramuscular injections of hCG, 1500 to 2000 IU 3 times a week for at least 6 months, as sperm production takes several months. After several months of hCG alone, if adequate spermatogenesis has not occurred, human menopausal gonadotropins or recombinant FSH can be added as an effective regimen in inducing spermatogenesis in male patients with idiopathic HH. However, there is insufficient information about the therapeutic or adverse effects of chronic hCG or recombinant FSH treatment of hypogonadism.

With hypothalamic disease, pulsatile subcutaneous or intravenous GnRH, delivered with an infusion pump and tubing (similar to an insulin pump), may be used to stimulate appropriate pituitary gonadotropin secretion. Obviously, this approach would not work in pituitary disease, and, like pituitary disease, would require months of therapy.

**NOVEL THERAPEUTICS**

Studies on estrogen feedback on the hypothalamic-pituitary axis in the human have



**Fig. 4.** The normal anatomy consists of the olfactory bulbs (blue arrows) located in the olfactory grooves of the anterior cranial fossa. The inferior surface of the frontal lobes usually consists gyrus rectus (R) separated from the medial orbital gyrus (M) by the olfactory sulcus (yellow arrow). These are absent in KS. (Courtesy of Dr Frank Gailard, Radiopaedia.org, Melbourne, Australia. rID: 6083.)

found that estrogen inhibits LH secretion by decreasing LH pulse amplitude and LH responsiveness to GnRH. Also, the use of aromatase inhibitors—a class of medication that functions to block the conversion of androgens to estrogens—was found to increase LH pulse frequency,<sup>52</sup> whereas testosterone level remains high. In addition, the increased gonadotropins further stimulate endogenous testosterone production, stimulate spermatogenesis, and improve male fertility. However there are risks in the chronic use of these medications, including bone loss, as most of the effect of testosterone on bone is mediated through estrogen.

Because hypogonadism is often associated with changes in the testosterone/estrogen ratio owing to increased levels of estrogens,<sup>53</sup> a different class of antiestrogens could also be used. Clomiphene citrate is a weak estrogen receptor antagonist and, thus, may be considered a selective estrogen receptor modulator. Clomiphene citrate competes with estradiol for the

estrogen receptors at the level of the hypothalamus and blocks the normal negative feedback mechanism of circulating estradiol on the hypothalamus, preventing estrogen from limiting the production of GnRH. The resulting increased amount of GnRH stimulates the pituitary gland to release more LH and FSH, resulting in an increase in testosterone and sperm production by the testis.<sup>54</sup> As sperm production proceeds over several months, a short course of clomiphene may increase sperm production enough to obtain sufficient sperm to achieve pregnancy. However, more prolonged use of clomiphene in men has not been studied sufficiently to recommend its chronic use to increase testosterone and spermatogenesis. In phase III trials, a similar drug, enclomiphene citrate, was found to similarly improve testosterone and spermatogenesis simultaneously in HH.<sup>55</sup>

In Klinefelter syndrome, isolated rests of areas with spermatogenesis have been successfully aspirated from the testes, especially in younger

men.<sup>56</sup> Even a few healthy sperm might be enough to achieve fertilization, through techniques such as ICSI (intracytoplasmic sperm insemination) in which a sperm is injected directly into an ovum obtained through in vitro fertilization.

## SUMMARY

Testosterone synthesis and male fertility are the results of the perfect coordination of the hypothalamic-pituitary-gonadal axis. A negative feedback finely controls the secretion of hormones at the 3 levels. Congenital or acquired disturbance at any level leads to an impairment of reproductive function and the clinical syndrome of hypogonadism. In some cases, this condition is reversible. Once the diagnosis is made, testosterone replacement therapy is the standard therapy; however, novel therapies may improve spermatogenesis while elevating testosterone levels.

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